SUMMARY OF SAFETY AND PROBABLE BENEFIT

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I. GENERAL INFORMATION

Device Generic Name: Interactive Wound and Burn Dressing

Device Trade Name: Dermagraft® , Human Fibroblast-Derived Dermal Substitute

Applicant's Name and Address: Ronald S. Warren, Executive Director
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10933 North Torrey Pines Road
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Humanitarian Device Exemption Number: H020004

Date of Humanitarian Use Device Designation: January 23, 2002

Date of Panel Recommendation: See section XI

Date Of GMP Inspection: January 11, 2001

Date Of Notice of Approval of Application: JUL - 7 2003

II. INTENDED USE / INDICATIONS

For the treatment of wounds related to dystrophic epidermolysis bullosa.

III. DEVICE DESCRIPTION

DERMAGRAFT® is a cryopreserved human fibroblast-derived dermal substitute; it is composed of fibroblasts, extracellular matrix, and a bioabsorbable scaffold. DERMAGRAFT is manufactured from human fibroblast cells derived from newborn foreskin tissue. During the manufacturing process, the human fibroblasts are seeded onto a bioabsorbable polyglactin mesh scaffold. The fibroblasts proliferate to fill the interstices of this scaffold and secrete human dermal collagen, matrix proteins, growth factors and cytokines, to create a three-dimensional human dermal substitute containing metabolically active, living cells. DERMAGRAFT does not contain macrophages, lymphocytes, blood vessels, or hair follicles.

DERMAGRAFT is supplied frozen in a clear bag containing one piece of approximately 2 in x 3 in (5 cm x 7.5 cm) for a single-use application.

IV. CONTRAINDICATIONS

- DERMAGRAFT is contraindicated for use in wounds that have signs of clinical infection.
- DERMAGRAFT is contraindicated for use in patients with known hypersensitivity to bovine products, as it may contain trace amounts of bovine proteins from the manufacturing medium and storage solution.

There are no warnings. The precautions can be found in the professional labeling.

V. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A. Epidermolysis Bullosa

Dermagraft® was tested in 6 recessive epidermolysis bullosa patients. One patient had an infection on the right shin at the time of application. The patient was treated with antibiotics and the infection resolved. The infection recurred at this site, but no other infections were seen. There were no malignancies reported in any of the 6 epidermolysis bullosa patients.

B. Diabetic Foot Ulcers

Dermagraft® was used in 389 patients in the PMA (P000036) studies for the treatment of full-thickness diabetic foot ulcers. The adverse events that occurred at frequencies of 5 percent or higher are listed in the table below. The most frequent adverse event was infection.

Adverse Events Reported in 5% or more of 389 Patients with Diabetic Foot Ulcers Treated with Dermagraft®

Adverse Event	Number of Patients	Percentage of Patients
Infection (study wound)	80	20.6
Skin dysfunction/blister	54	13.9
Infection (non-study wound)	50	12.6
Surgeries involving skin ulcer	48	12.3
Abnormal laboratory Result (Chem., hematology or urinalysis)	43	11.1
Wound enlargement (non-study ulcer)	42	10.8
Cellulitis (study wound)	37	9.5
Accidental injury	34	8.7
Osteomyelitis	31	8.0
Pain	30	7.7
Peripheral edema (localized swelling)	29	7.5
Cellulitis (non-study wound)	25	6.4
Flu syndrome	22	5.7
Pharyngitis/URI	20	5.1

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Epidermolysis bullosa is treated with a wide range of palliative dressings. The range of dressings is broad and includes variations designed to address different aspects of wound management. Wound contact layers, for example, are designed to allow fluids and oxygen to pass from and to the wound, but are made of materials that will not disturb the newly formed skin. The materials used are commonly silicone or high-density polyethylene. Vaseline-coated gauze is non-adherent, and can be use as either a primary or a secondary dressing. Hydrogels contain large amounts of water that provides a moist wound environment which is optimal for wound healing. Gauze is commonly used as one of the dressing components.

Some collagen dressings are presumed to help the wound form collagen fibers. The problem with dystrophic epidermolysis is that these patients cannot make the correct form of collagen, collagen VII, and collagen dressings do not provide significant amounts of human collagen VII.

Other palliative treatments include wrapping fingers to delay the webbing process. Vaseline gauze may be used for this purpose. In addition to wound management, other important considerations in the care of these patients include infection control, surgical management when required, and nutritional support. Surveillance for squamous cell carcinoma is required because this frequently occurs in the recessive form DEB.

VII. MARKETING HISTORY

Dermagraft was approved in the United States for use on diabetic foot ulcers on September 28th, 2001, and has been marketed for diabetic foot ulcers since that time. The device is now available for commercial distribution in 10 countries in addition to the United States.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

A. Selected Pre-Clinical Characterization and Performance Studies

Study	Results/Conclusions
Development and Characterization	
Assessment of the in vitro aging of fibroblasts in DERMAGRAFT	No significant loss of proliferative capacity before 45 doublings was observed and cells continued to grow for approximately 60 doublings. Fibroblasts used in the manufacture of DERMAGRAFT are within a region of the cultural life span in which synthetic and proliferative activities may be expected to be consistent.
Evaluation of DERMAGRAFT cell banks for the presence of other cell types	Flow cytometric analyses (fluorescence activated cell sorting [FACS]) did not detect the presence of keratinocytes in the fibroblast cell banks.
Feasibility Study - Grafting of a Cultured Skin Equivalent grown on mesh framework (Nylon) into full thickness wounds in Rats	Results showed incorporation of the grafts into the wounds and complete epithelialization. Histological examination revealed keratinocytes, fibroblasts.

	collagen, adipocytes and smooth muscle fibers arranged in a natural configuration around nylon mesh fibers.
DERMAGRAFT as a Dermal Replacement in Mini-Pigs to determine if the device cultured with human fibroblasts would incorporate safely into full thickness wounds.	Evidence of the safety and biocompatibility of a device cultured with human fibroblasts was established in a porcine model with implants over six months.
Athymic Mouse Studies to support DERMAGRAFT in the treatment of full thickness burn wounds and evaluate the viability of DERMAGRAFT with respect to wound healing	Demonstrated the ability of the device to support healing and re-epithelialization of meshed, split-thickness human cadaver skin placed on surgically excised wounds in mice.

Development and Characterization (cont'd.)	
Stimulation of Angiogenesis in the Chick Chorioallantoic Membrane (CAM) assay	Three dimensional fibroblast cultures induced vessel development in the CAM to a greater extent than control. Capillary development is characteristic of VEGF induced angiogenesis. Preincubation of the fibroblast culture with anti-VEGF neutralizing antibody reduced the angiogenic activity to control values.
Expression of Angiogenic Growth Factors	VEGF and HGF mRNA was expressed in DERMAGRAFT. Also detected were PDGF A-chain, $TGF\beta_1$,G-CSF and angiopoietin I.
Splice Variants of VEGF in Fibroblasts	Splice variants of VEGF corresponding to the diffusable and extracellular matrix-binding forms of VEGF were detected in RNA isolated from DERMAGRAFT via PCR technique.

Immunology	
Persistence	PCR testing of biopsies in venous ulcers detected DERMAGRAFT cells in human patients up to 6 months after implantation.
Response of DERMAGRAFT to γ-interferon	In scaffold-based (DERMAGRAFT) three dimensional fibroblast cell cultures, γ-interferon caused little induction of CD40 and HLA-DR antigens whereas all cells upregulated the expression of HLA I antigen. Fibroblast cells grown on collagen gel or in monolayer culture, in contrast, upregulated both the expression of HLA I, HLA II and CD40 antigens in response to γ-interferon.
Immunogenicity	Immunogenicity via histological assessment displayed no findings suggestive of an immune response; The potential for DERMAGRAFT to elicit an immune response was evaluated by examining the baseline and terminal sera of patients enrolled in a clinical trial for DERMAGRAFT using Western Blot technique. No clinically significant antibody response to DERMAGRAFT was observed.

B. The biocompatibility studies.

Toxicology Studies **(sterilized plastics and polymeric components that have direct or indirect product contact)**	
Cytotoxicity	No reactivity. Non-cytotoxic.
Intracutaneous Reactivity	No reactivity. Non-irritant.
Systemic Toxicity	No reactivity. Non-toxic.

Toxicology and Safety Studies (DERMAGRAFT)	
Genotoxicity assays: Ames Mutagenicity Mouse Lymphoma Mutagenesis	 Pass. Non-mutagenic. Pass. Non-mutagenic.
Tumorigenicity	Evaluation of tumor formation of end of production stage fibroblasts in nude athymic mice revealed the cells to be non-tumorigenic.
Karyological analyses	Karyological analyses of the fibroblast cells used in manufacture of DERMAGRAFT revealed a limited number of chromosomal changes. These same cells did not exhibit a transformed phenotype in *in vitro* nor in *in vivo* tumorigenicity assays. Cell growth characteristics, i.e., morphology, cell doubling time, and substratum adherence, were monitored and judged to be consistent through end of production stage cells. DNA marker identification evaluations indicated that the cell bank was from a sole donor.

Stability/Shipping Studies	
Stability of the device when stored at –70.	Stability testing via assays to evaluate the product following real-time aging. The device when stored at -70°C meets requirements for sterility and product specifications for periods up to seven months.
Validation study to verify that the manufacturing process consistently produces DERMAGRAFT.	Three consecutive qualified validation lots passed initial release criteria and established a minimum of three months acceptable stability. Long term testing results establish stability of the product for up to six months when stored at -75°C ± 10°C was obtained.
Safe shipping of DERMAGRAFT	Thermal, impact and airfreight shipping tests were conducted to assure storage temperature requirements are maintained and all product release criteria are met with respect to sterility, viability, collagen and DNA. DERMAGRAFT can be safely shipped to domestic and international shipping destinations.

C. Sterility Testing

The fibroblast cells, from which DERMAGRAFT is manufactured, are from human infant foreskin tissue. A comprehensive medical history of the mother is taken and maternal serum is screened for the presence of HIV-1, HIV-2, HTLV-I, Hepatitis B core antigen, Hepatitis B surface antigen, Hepatitis C, non-A/non-B Hepatitis (detection via Alanine Aminotransferase (ALT) activity), Cytomegalovirus (CMV), and Syphilis. Additionally, the human foreskin fibroblasts used to form DERMAGRAFT are derived from cell banks which are tested for the presence of HIV-1, HIV-2, HTLV-I, HTLV-II, Hepatitis B, Hepatitis C, Herpes Simplex Virus (HSV) Types 1 and 2, CMV, Epstein Barr Virus (EBV), Adenovirus, Adventitious Viral Contaminants (*In Vitro* and *In Vivo*

Assays), b virus particles by Electron Microscopy (EM), retrovirus by RT-PCR, mycoplasma, bacteria, and fungi.

Product manufacture includes the use of bovine calf serum (BCS). The BCS is provided with a certificate of analysis documenting the viruses screened for in the serum and that it is obtained from a Bovine Spongiform Encephalopathy (BSE)-free country. The sponsor, upon receipt of BCS, tests the serum for sterility, endotoxin and mycoplasma. The serum is functionally assessed by a growth promotion test.

To maintain cell viability the product is aseptically manufactured, but not terminally sterilized. DERMAGRAFT is shipped after quarantine pending results of sterility (14 day), endotoxin and mycoplasma testing.

IX. SUMMARY CLINICAL STUDIES

The clinical data presented is based on retrospective data obtained from six recessive epidermolysis patients treated with Dermagraft in an uncontrolled study. The wounds were scored in 6 general body areas: the leg, foot, arm, buttocks, hands, and back.

A. Effectiveness Outcomes:

Epidermal coverage was reported as ranging between 75 and 100% after 8 weeks of treatment after the application of Dermagraft.

B. Device Safety

One patient treated with Dermagraft had an infection when entering the study. The infection resolved, but recurred in the presence Dermagraft.

No adverse events were detected in the 6 patients studied. There were no cases of squamous cell carcinoma in any of the 6 patients studied.

In the PMA (P000036) diabetic foot ulcer study of 389 patients, the most frequent adverse events were infection in 20% of the patients and skin dysfunction or blistering in 13.9% of the patients.

C. Immune Response

Findings in the diabetic foot ulcer study have not revealed any significant clinical manifestations of product-related immunological reactions. The sera of a number of diabetic foot ulcer patients treated with Dermagraft were examined by the Western Blot technique. No significant antibody response to Dermagraft was observed in patients treated with 8 pieces of Dermagraft.

X. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINCIAL STUDIES

The pre-clinical safety studies demonstrate the biocompatibility of the device and its components. Further support for the safety of Dermagraft® may be inferred from the clinical data available on its use in the treatment of diabetic foot ulcers. The ability of the device to support healing was demonstrated in athymic mouse studies and as a dermal replacement in Mini-pigs.

The retrospective uncontrolled 6-patient series submitted on recessive epidermolysis bullosa (EB) patients is not adequate to definitively establish the safety and effectiveness of the device for the treatment of wounds related to EB. However, the data do demonstrate that the device can serve as a beneficial adjunct to the wound healing process in combination with infection control, surgical management, and nutritional support. The only adverse event reported was an infection, which was present when the patient presented. There were no other infections.

In conclusion, the preclinical and performance studies provide reasonable assurance that the device is appropriate for use on wounds in EB patients. The limited clinical data suggest that the device will not expose patients to unreasonable or significant risks of illness or injury, especially considering the probable risks and benefits of currently available devices or alternative treatments for this disease.

XI. PANEL RECOMMENDATION

The General and Plastic Surgery Devices Panel did not review this application, because the panel had input on a similar device for a different intended use.

XII. CDRH DECISION

CDRH has determined that on the basis of the preclinical and limited clinical data submitted in this HDE, Dermagraft® will not expose patients to an unreasonable risk of illness or injury, and that the probable benefit to health from using the device outweighs the risk of injury and issued an approval order on JUL - 7 2003.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See professional labeling (Attachment 1)

Warnings, hazards to health with the use of the Device: See indications, contraindications warnings, precautions and adverse events in the labeling.

Information for the Patient: A patient information brochure is attached.